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EXAMINER	
ANDERSON, JAMES D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/856,282	DAVIS, BONNIE M	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10-21,24-26 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,10-21,24-26 and 29-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5, and 10-21, 24-26, and 29-42 are presented for examination

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2007 has been entered.

Status of the Claims

Applicants' amendment filed 10/29/2007 has been received and entered into the application. Accordingly, claims 1, 15, 21, and 41 have been amended and claim 42 has been added.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby

withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Priority

This application is a 371 of PCT/US99/27481, filed 11/19/1999.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Response to Arguments

Applicant's arguments with respect to claims 1, 3-5, and 10-21, 24-26, and 29-42 have been considered but are moot in view of the new ground(s) of rejection.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 contains the trade names Probanthine and Robinul. M.P.E.P. § 2173.05(u) states, "It is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus a trademark or trade name does not identify or describe the goods associated with the trademark or trade name." If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982).

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, and 10-21, 24-26, and 29-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of*

California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims contain functional language that fails to define what the claimed pharmaceutical compositions are made of. An example of such functional language is the following:

> "...wherein acetylcholinesterase inhibitor is formulated so as to delay its activity..." (claims 1 and 21).

In the above example, there is no description of what the pharmaceutical composition *contains* "so as to delay" the activity of the acetylcholinesterase inhibitor for a predetermined time period

of from four to twelve hours as recited in the claims. For example, there are no excipients, sustained-release coatings, binders, surfactants, etc. recited in the claims or specification. As such, the claims lack written description because the claimed pharmaceutical compositions are not adequately described in a manner that would indicate what the compositions are composed of, other than the claimed acetylcholinesterase inhibitor(s).

The lack of written description of the instantly claimed compositions is further compounded by the fact that the compositions require specific delay periods of the active agents. It is noted that no specific formulations are disclosed in the specification and that Applicants have not described any specific examples of excipients, carriers, or extended release coatings that would result in the claimed delay periods of the active agents.

Aside from the very limited discussion provided in the specification, Applicants provide no direction as to (a) what excipients and extended release coatings out of all possible excipients and extended release coatings that exist in the art would have been reasonably expected to result in the claimed delay periods of the active agents and (b) which of those excipients and extended release coatings actually *do* result in the claimed delay periods of the active agents without having to execute hit or miss testing practices in order to make such a determination.

The need for testing amongst varying species and amounts of excipients and release coatings to determine what formulations would result in the claimed delay periods of the active agents demonstrates that Applicants were not in possession of the full scope of the compositions and methods now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for

patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of specific active agents and preferable dosages, it remains that the claims recite a solely functional pharmaceutical composition. With the exception of the specific active agents recited in the claims, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other excipients, carriers, in-actives, and extended release coatings that may result in the claimed delay periods of the active agents, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention. It is also noted that the specification provides no examples of any particular compositions as recited in the instant claims.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other excipients, carriers, in-actives, and extended release coatings that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such excipients, carriers, in-actives, and extended release coatings, and, therefore, did not have written description of the full scope of the compositions now claimed.

Further, though Applicants have limited the claimed compositions to those that have particular delay periods of inactivity of the active agents, it remains that Applicants have not appropriately defined the metes and bounds of the claimed compositions, even when limited by function (step-plus-function form). As taught in the MPEP at § 2163, step-plus-function claims are not adequately described if "the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application fails to meet these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims recite dosage forms comprising a centrally-acting acetylcholinesterase inhibitor (*e.g.*, galanthamine) formulated so as to delay the activity of the acetylcholinesterase inhibitor for a predetermined period of from four to twelve hours.

Claims 1, 3-5, 10-19, 21, 24-26, and 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988) (prior art of record) in view of **Conte *et al***. (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023) (prior art of record).

WO 88/08708 teaches compounds of formula (I) for use in the treatment of Alzheimer's disease (Abstract). Such compounds are galanthamine-analogues as recited in claims 1, 3-5, and 10-19 (pages 9-17). The compounds of the invention are inhibitors of acetylcholinesterase (page 38). Compositions for administration to patients having Alzheimer's disease, including sustained release delivery formulations, are taught at page 24, first and second paragraph. With respect to the claimed half life of from one to eleven hours as recited in the instant claims, the half life of any compound is a property of that compound and thus not separable from the compound itself. Therefore, because WO 88/08708 teaches the claimed compounds, the properties of these compounds that Applicants recite in the instant claims are necessarily present. WO 88/08708 does not teach a formulation wherein acetylcholinesterase inhibition is avoided for a predetermined period of from four to twelve hours as recited in the instant claims.

However, Conte *et al*. teach methods of formulating pharmaceutical active agents in press-coated tablets for time-programmed release of drugs (Abstract). The delay in release start is taught to not be influenced by the core composition and depends only on the shell formulation (*id*.). Suitable drugs for such time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (*e.g*., psychotropic active drugs) (page 1017, left column, second full paragraph). The press-coated tablets taught in Conte *et al*. release drugs at a specific rate, but the release starts only after a well defined period of time (page 1017, right column, first full paragraph). With respect to the delay periods recited in claims 1 and 3-4 (i.e., 4 to 12 hours, 6 to 9 hours, or 8 to 12 hours), Conte *et al*. teach such delay periods, *e.g*., 240 minutes, 480 minutes, and 720 minutes (Figures 6, 7, and 8).

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate galanthamine or galanthamine-analogues as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that WO 88/08708 teaches that galanthamine was known in the art as an agent useful in treating Alzheimer's disease "and related dementias" (page

1) and inhibits acetylcholinesterase (page 38), a reasonable interpretation of which is that galanthamine is a psychotropic drug and thus reasonably suggested by Conte *et al.*[1] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping. As such, Conte *et al.* provides methods of formulating compositions that will aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

Claims 1, 3-5, 20-21, 24-26 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Conte *et al.*** in view of **Nordberg *et al.*** (Drug Safety, 1998, vol. 19, no. 6, pages 465-480) (newly cited – Abstract attached herein).

Conte *et al.* teach as discussed *supra*. The reference does not teach the acetylcholinesterase inhibitor, rivastigmine, as specifically recited in claims 20 and 38.

However, Nordberg *et al.* compare the tolerability and pharmacology of cholinesterase inhibitors in the treatment of Alzheimer's disease. In this regard, the reference teaches that cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease and that three cholinesterase inhibitors are in clinical use: tacrine, donepezil, and rivastigmine (Abstract). Further, Nordberg *et al.* teach that other cholinesterase inhibitors such as galanthamine (also recited in the instant claims) are under clinical evaluation (*id.*).

[1] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the central nervous system where it alters brain function.

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate rivastigmine as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that Nordberg *et al*. teach that rivastigmine inhibits acetylcholinesterase and was known in the art as an agent useful in treating Alzheimer's disease (Abstract; pages 475-476), a reasonable interpretation of which is that rivastigmine is a psychotropic drug and thus reasonably suggested by Conte *et al*.[2] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's dementia or behavioral abnormalities would not be in need of medication while they are sleeping. As such, Conte *et al*. provides methods of formulating compositions that will also aid in patient compliance, *i.e*., a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

[2] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the central nervous system where it alters brain function.

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** and **Conte *et al***. as applied to claims 1, 3-5, 10-19, 21, 24-26, and 29-37 above, and further in view of **Faber *et al.*** (Am. J. Psychiatry, Jan. 1999, vol. 156, no. 1, page 156) (newly cited).

WO 88/08708 and Conte *et al*. teach as discussed *supra*. The references do not teach the administering of a compound (*e.g*., Probanthine) that reduces the peripheral effects of the claimed acetylcholinesterase inhibitors.

However, Faber *et al*. teach that propantheline[3], a peripherally acting anticholinergic medication, reduces the peripheral cholinergic activity caused by adminsitration of the cholinesterase inhibititor tacrine (page 156, left column). Based on the results of their study, the authors suggest the use of adjunctive propantheline in patients with cholinergic effects from tacrine or other cholinesterase inhibitors.

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer acetylcholinesterase inhibitors as recited in the instant claims in conjunction with a compound that reduces its peripheral effects, such as propantheline as motivated and suggested by Faber *et al*.

[3] Propantheline is the common chemical name of the drug sold as Pro-Banthine.

Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** and **Conte *et al***. as applied to claims 1, 3-5, 10-19, 21, 24-26, and 29-37 above, and further in view of **Moormann** (USP No. 5,643,905) (previously cited).

WO 88/08708 and Conte *et al*. teach as discussed *supra*. The references do not teach the administering of the formulations suggested therein so as to avoid release of the acetylcholinesterase inhibitor for the next anticipated sleep time (claim 41) or to allow a patient's central nervous system to become hypocholinergic during the period of desired sleep so as to avoid sleep disturbances during hours of desired sleep (claim 42).

However, Moorman teaches that galanthamine is an anticholinesterase inhibitor that can pass the blood-brain barrier and antagonize the cerebral effects of anticholinergic poisons. In addition, Moorman discloses that galanthamine promotes awakening from twilight sleep (col. 2). Here, the skilled artisan is provided with the necessary motivation to develop controlled release formulations of galanthamine (such as those suggested and motivated by WO '708 in view of Conte *et al*.) in order to avoid waking a patient from sleep.

Accordingly, the skilled artisan would have been imbued with at least a reasonable expectation that delaying the release of galanthamine or analogues thereof during periods of sleep would avoid waking a patient from sleep since no anticholinesterase activity would occur.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

1) **USP No. 6,565,883** (Issued May 20, 2003; Filed Apr. 8, 2002) and **WO 00/19985** (Published April 13, 2000) teach pharmaceutical compositions comprising rivastigmine capable of releasing the active agent in a time-controlled manner, *e.g.*, controlling the time until the release of active agent (lag time or delay time);

2) **Riemman *et al***. (Psychiatry Research, 1994, vol. 51, no. 3, pages 253-267) (Abstract attached) provide a study showing the effects of the cholinesterase inhibitor galanthamine hydrobromide on normal sleep.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614